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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,872	12/06/2004	Hubertus Johannes Marie Op Den Camp	OP DEN CAMP-1	1317

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EXAMINER	
FRONDA, CHRISTIAN L	
ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
06/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,872	OP DEN CAMP ET AL.	
	Examiner	Art Unit	
	CHRISTIAN L. FRONDA	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-20 and 24-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-20,25,27 and 28* is/are rejected.

7)☒ Claim(s) *24 and 26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/31/2008 has been entered.

2. Claims 1-4, 6-20, and 24-28 are pending and under consideration in this Office Action. New rejections and grounds of rejection are presented in the instant Office Action.

Claim Rejections - 35 U.S.C. § 112, 1st Paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-4, 6-20, 25, 27, and 28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants are directed toward the current USPTO Written Description Training Materials made available to the public on 04/11/2008 for information regarding examination of patent claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph.

The claims are genus claims encompassing a genus of nucleic acids comprising a nucleotide sequence encoding xylose isomerase having an amino acid sequence which is 95%

identical to SEQ ID NO: 1. The scope of the genus includes many members with widely differing nucleotide and/or amino acid sequences and structures, where the genus is highly variable because a significant number of structural and biological differences between genus members exists.

The claimed nucleic acid comprising a nucleotide sequence encoding xylose isomerase represent a partial structure. There is no teaching in the specification regarding which amino acids residues in the claimed polypeptides that can be altered (amino acid substitutions, deletions, additions, insertions, and combinations thereof) or modified while maintaining catalytic activity. Thus, one of ordinary skill in the art would not be able to identify the specific amino acid residues in SEQ ID NO: 1 that can be altered as claimed without further testing, where the polypeptides still has xylose isomerase activity.

The specification discloses the polynucleotide consisting of SEQ ID NO: 2 encoding a polypeptide consisting of SEQ ID NO: 1 xylose isomerase activity. The specification, however, does not describe and define any structural features, nucleotide and/or amino acid sequences, and/or biological functions that are commonly possessed by members of the genus. The specification dos not provide a correlation between any structure, other than the above mentioned SEQ ID NO: 2 encoding SEQ ID NO: 1, and xylose isomerase based on which those of ordinary skill in the art could predict which amino acids can vary from without losing the catalytic activity. Further, there is no art-recognized correlation between any structure and xylose isomerase based on which those of ordinary skill in the art could predict which amino acids can vary without losing the catalytic activity. There is no information about which amino acids can vary from SEQ ID NO: 1 but still retain xylose isomerase activity. Accordingly, there is no information regarding the nucleotide sequence and nucleotide composition of the corresponding encoding nucleic acids of the genus.

MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification fails to disclose additional nucleic acids as claimed. As such the disclosure of the above mentioned SEQ ID NO: 2 encoding SEQ ID

NO: 1 is insufficient to be representative of the attributes and features common to all the members of the claimed genus.

Vas-Cath, Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class, where the specification provided only the bovine sequence. In view of the above considerations, one of skill in the art would not recognize that applicants were in possession of the claimed genus.

5. Claims 1-4, 6-20, 25, 27, and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a cultured isolated eukaryotic cell transformed with a nucleic acid construct comprising a nucleotide sequence encoding a xylose isomerase comprising the amino acid sequence of SEQ ID NO: 1; and a process for producing ethanol, lactic acid, acetic acid, succinic acid, an amino acid, 1,3-propanediol, ethylene, glycerol, a β-lactam, or cephalosporin comprising fermenting a medium containing a source of xylose with the said eukaryotic cell; does not reasonably provide enablement any other embodiment as recited in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

According to MPEP 2164.01(a), factors considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue” include, but are not limited to: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The

quantity of experimentation needed to make or use the invention based on the content of the disclosure.

MPEP§ 2164.04 states that while the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection. The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims. Accordingly, the factors most relevant to the instant rejection are addressed in detail below.

The nature and breadth of the claims encompass any cultured eukaryotic host cell transformed with any nucleic acid construct comprising any nucleotide sequence encoding any xylose isomerase comprising an amino acid sequence that is at least 95% identical to SEQ ID NO: 1.

The previously enclosed reference of Chica et al. (Curr Opin Biotechnol. 2005 Aug;16(4):378-84; reference of record) teaches that the complexity of the structure/function relationship in enzymes has proven to be the factor limiting the general application of rational enzyme modification and design, where rational enzyme modification and design requires in-depth understanding of structure/function.

The specification provides guidance, prediction, and working examples for the isolated polynucleotide from *Piromyces* sp. E2 (ATCC 76762) consisting of SEQ ID NO: 2 encoding a xylose isomerase consisting of the amino acid sequence of SEQ ID NO: 1, yeast expression vectors containing said isolated polynucleotide, yeast host cells transformed with said expression vectors, and growth of said yeast host cells on xylose. However, the specification does not provide guidance, prediction, and working examples for making and/or using the invention as claimed.

The specification, however, does not provide a correlation between any structure, other than the above mentioned SEQ ID NO: 2 encoding SEQ ID NO: 1, and xylose isomerase activity based on which those of ordinary skill in the art could predict which amino acids can vary from without losing the catalytic activity. Further, there is no art-recognized correlation between any

structure and xylose isomerase activity based on which those of ordinary skill in the art could predict which amino acids can vary without losing the catalytic activity. There is no information about which amino acids can vary from SEQ ID NO: 1 but still retain xylose isomerase activity. Accordingly, there is no information regarding the nucleotide sequence and nucleotide composition of the corresponding encoding nucleic acid.

Thus, one must perform an enormous amount of trial and error experimentation to search and screen for the claimed nucleic acid from any biological source or synthesize the nucleic acid as claimed and determine if the nucleic acid will encode a polypeptide that has xylose isomerase activity. General teaching regarding screening and searching for the claimed invention using activity assays stated in the specification is not guidance for making the claimed invention.

Therefore, in view of the overly broad scope of the claims, the specification's lack of specific guidance and prediction, the specification's lack of additional working examples, and the amount of experimentation required; it would require undue experimentation for a skilled artisan to make and use the claimed invention. Without sufficient guidance, the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988).

Claim Rejections - 35 U.S.C. § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-4 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guan et al. (US Patent 5,643,758; published 07/01/1997; reference of record) or Karlsson et al. (Eur J Biochem. 2001 Dec;268(24):6498-507; reference of record) in view of Accession Q9P8C9 (published 2000-10-01; reference of record).

Guan et al. teach expression vectors containing promoters, prokaryotic host cells such as *E. coli* and eukaryotic host cells such as yeast, and methods for making, expressing, isolating, and purifying any protein fused to the *E.coli* maltose binding protein (MBP) using the said expression vectors, prokaryotic and eukaryotic host cells such as yeast; and that these methods and products are useful for purifying virtually any hybrid polypeptide molecule employing recombinant techniques (see entire patent).

Karlsson et al. teach the filamentous fungus *Trichoderma reesei* host cell transformed with an expression vector containing a polynucleotide encoding Ce161A (EG IV) (see entire publication).

The teachings of Guan et al. and Karlsson et al. differs from the claims in that the yeast host cell or the filamentous fungus *Trichoderma reesei* host cell not transformed with a polynucleotide encoding a xylose isomerase comprising an amino acid sequence that has at least 70% , 80%, 90%, 95% identity to SEQ ID NO: 1 or is SEQ ID NO: 1.

Accession Q9P8C9 teaches a xylose isomerase from *Piromyces sp.* E2 having an amino acid sequence that is 99% identical to SEQ ID NO: 1 (see attached alignment; reference of record).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use transform the yeast host cell taught by Guan et al. or *Trichoderma reesei* host cell taught by Karlsson et al. with the polynucleotide encoding the xylose isomerase taught by Accession Q9P8C9 having an amino acid sequence that is 99% identical to SEQ ID NO: 1. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to express and purify the xylose isomerase taught by Accession Q9P8C9. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for success because recombinant molecular biology techniques for heterologous or homologous expression of proteins is well developed in the art.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made, and was as a whole clearly *prima facie* obvious.

The arguments filed 03/31/2008 and Declaration of Jan A.M. de Bont pursuant to 37 C.F.R. §1.132 have been fully considered but are not persuasive. In regard to the arguments that motivation for combining the references has not been provided, according to MPEP 2143:

> "Exemplary rationales that may support a conclusion of obviousness include:
>
> (A) Combining prior art elements according to known methods to yield predictable results;
>
> (B) Simple substitution of one known element for another to obtain predictable results;
>
> (C) Use of known technique to improve similar devices (methods, or products) in the same way;
>
> (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
>
> (E) " Obvious to try " – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
>
> (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;
>
> (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.
>
> Note that the list of rationales provided is not intended to be an all-inclusive list. Other rationales to support a conclusion of obviousness may be relied upon by Office personnel."

Furthermore, according to MPEP 2144 [R-5]:

> "It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. >See, e.g., *In re Kahn*, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)."

Combining the teachings of the references as previously stated by using the products and methods taught by Guan et al. and Karlsson et al. with the polynucleotide encoding the xylose isomerase taught by Accession Q9P8C9 having an amino acid sequence that is 99% identical to SEQ ID NO: 1 of the instant application would yield the predictable result of the recombinant expression and purification of xylose isomerase taught by Accession Q9P8C9, where recombinant expression and purification of proteins have the well recognized and well established advantage of production of large, purified amounts of the desired proteins.

In response to the arguments that there is no expectation of success, the instant application shows successful expression of the xylose isomerase consisting of SEQ ID NO: 1 in

yeast cells. It is well known in the art that yeast cells have been used to recombinant express and purify desired proteins. Given that the combination of references stated above, the knowledge of one of ordinary skill in the art regarding recombinant expression of purification of desired proteins in eukaryotic cells such as yeast and means of optimizing expression and purification of the desired proteins in yeast, and the specification showing the successful expression of the xylose isomerase consisting of SEQ ID NO: 1 in yeast cells, one of ordinary skill in the art would have a reasonable expectation of success in making the claimed invention. According to MPEP 2143.02 [R-6]:

> "A rationale to support a conclusion that a claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1395 (2007); *Sakraida v. AG Pro, Inc.*, 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); *Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp.*, 340 U.S. 147, 152, 87 USPQ 303, 306 (1950)."

Accordingly, the claimed invention was within the ordinary skill in the art to make and use at the time was made, and was as a whole clearly *prima facie* obvious.

Conclusion

8. No claim is allowed.

9. Claims 24 and 26 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929.

The examiner can normally be reached Monday-Thursday and alternate Fridays between 9:00AM - 6:30PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed can be reached on (571)272-0934. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

11. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christian L. Fronda/
Patent Examiner
Art Unit 1652